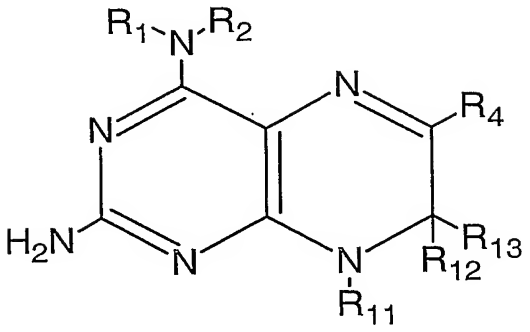
Claims

1. A compound of formula I:



(I)

wherein

R_1 is hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkenyl, (C_1-C_{20})-alkynyl, preferably (C_1-C_{10})-alkyl, cycloalkyl, cycloalkenyl, preferably (C_3-C_8)-cycloalkyl, cycloalkylalkyl, aryl, alkylaryl, preferably (C_1-C_3)-alkylaryl or arylalkyl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6,

R_2 is, independently of R_1, hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkenyl, (C_1-C_{20})-alkynyl, preferably (C_1-C_{10})-alkyl, cycloalkyl, cycloalkenyl, preferably (C_3-C_8)-cycloalkyl, cycloalkylalkyl, aryl, alkylaryl, preferably (C_1-C_3)-alkylaryl, or arylalkyl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6, or

R_1 and R_2 may, together with the nitrogen atom bearing them, form a 3-8-membered ring which may optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and which is optionally substituted by one or more radicals, preferably R_6 radicals,

R_4 is $(C_1\text{-}C_{20})$-alkyl, $(C_1\text{-}C_{20})$-alkenyl, $(C_1\text{-}C_{20})$-alkynyl, preferably $(C_1\text{-}C_{10})$-alkyl, cycloalkyl, cycloalkenyl, preferably $(C_3\text{-}C_8)$-cycloalkyl, cycloalkylalkyl, aryl or $(C_1\text{-}C_{20})$-alkylaryl, preferably $(C_1\text{-}C_3)$-alkylaryl, arylalkyl, -CO-O-alkyl, preferably -CO-O-$(C_1\text{-}C_5)$-alkyl, -CO-O-aryl, -CO-alkyl, preferably -CO-$(C_1\text{-}C_5)$-alkyl or -CO-aryl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, in particular by substituents R_7,

R_6 is -F, -Cl, -Br, -I, -OH, -O-$(C_1\text{-}C_{10})$-alkyl, -O-phenyl, -O-CO-$(C_1\text{-}C_{10})$-alkyl, -O-CO-aryl, $-NR_8R_9$, oxo, phenyl, -CO-$(C_1\text{-}C_5)$-alkyl, $-CF_3$, -CN, $-CONR_8R_9$, -COOH, -CO-O-$(C_1\text{-}C_5)$-alkyl, -CO-O-aryl, $-S(O)_n$-$(C_1\text{-}C_5)$-alkyl, or $-SO_2$-NR_8R_9,

R_7 has, independently of R_6, one of the meanings of R_6,

R_8 is hydrogen or $(C_1\text{-}C_{20})$-alkyl, preferably $(C_1\text{-}C_5)$-alkyl,

R_9 is hydrogen, $(C_1\text{-}C_{20})$-alkyl, preferably $(C_1\text{-}C_5)$-alkyl or aryl, preferably phenyl,

R_{11} is hydrogen, $(C_1\text{-}C_{20})$-alkyl, preferably $(C_1\text{-}C_5)$-alkyl, aryl, -CO-alkyl, -CO-aryl, where the organic radicals, preferably the alkyl and/or aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6

R_{12} is hydrogen, $(C_1\text{-}C_{10})$-alkyl, preferably $(C_1\text{-}C_5)$-alkyl, aryl, -O-$(C_1\text{-}C_{10})$-alkyl, -O-phenyl, -O-CO-$(C_1\text{-}C_{10})$-alkyl, -O-CO-aryl, $-NR_8R_9$, phenyl, -CO-$(C_1\text{-}C_{10})$-alkyl, preferably –CO-$(C_1\text{-}C_{10})$alkyl, $-CF_3$, -CN, $-CONR_8R_9$, -COOH, -CO-O-$(C_1\text{-}C_{10})$-alkyl, preferably CO-O-$(C_1\text{-}C_{10})$alkyl, -CO-O-aryl, -F or –Cl

R_{13} has, independently of R_{12}, one of the meanings of R_{12}

aryl is preferably phenyl, naphthyl or heteroaryl, each of which may be unsubstituted or substituted, for example may be substituted by one or more identical or different substituents from the series halogen, $(C_1\text{-}C_{20})$-alkyl, preferably $(C_1\text{-}C_5)$-alkyl or phenyl, -OH, -O-$(C_1\text{-}C_{20})$-alkyl, preferably -O-$(C_1\text{-}C_5)$-alkyl, $(C_1\text{-}C_{20})$-

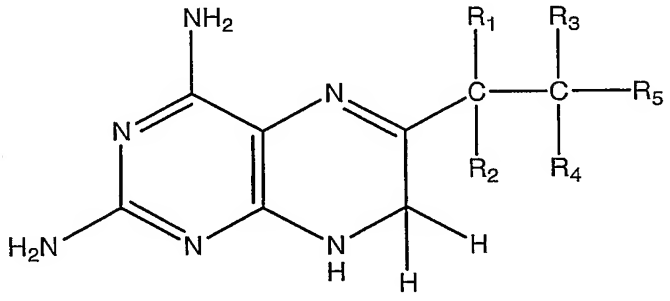
alkylenedioxy, preferably (C_1-C_2)-alkylenedioxy, -N_8R_9, -NO_2, -CO-(C_1-C_5)-alkyl, -CF_3, -CN, -$CONR_8R_9$, -COOH, -CO-O-(C_1-C_5)-alkyl, -$S(O)_n$-(C_1-C_5)-alkyl, -SO_2-NR_8R_9,

heteroaryl is a 5- to 7-membered unsaturated heterocycle which contains one or more heteroatoms from the series O, N, S,

n is 0, 1 or 2,

in all their stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and their physiologically tolerated salts, hydrates and esters.

with the proviso that compounds of the formula (Ia)



(Ia) are excluded,

wherein in formula (Ia) R_1, R_2, R_3 and R_4 are independently from each other H or OH, R_5 is H, CH_3, CH_2OH, CHO or a lower (C_1-C_9) alkyl radical, which can be a straight or a branched chain, as well as $(CH(OH))_n$-Y or $(CH(OH))_n$-$(CH_2)_m$-W, wherein Y is hydrogen or a lower alkyl (C_1-C_9) radical, W is hydrogen or a hydroxyl group, an n and m are independently from each other 1-20.

2. The compound of claim 1, wherein

R_1 is hydrogen,

R_2 is hydrogen, (C_1-C_{20})-alkyl or cycloalkylalkyl,

R_4 is phenyl, (C_1-C_{20})-alkylphenyl or (C_{12}-C_{20})-alkyl which is optionally substituted with -OH, alkyloxy or halogen, and wherein

R_{11}, R_{12} and R_{13} are independently of each other either hydrogen or methyl.

3. The compound of claim 2, wherein

R_1 is cycloalkylalkyl, optionally substituted with (C_1-C_5)-alkyl, or (C_1-C_5)-O-alkyl,

R_2 is hydrogen,

R_4 is 1,2-dihydroxypropyl and

R_{11}, R_{12} and R_{13} are independently of each other either hydrogen or methyl.

4. The compound of claim 3, wherein R1 is cyclohexylmethyl or cylcohexylethyl.

5. The compound of claim 1, wherein

R_1 is hydrogen,

R_2 is hydrogen, (C_1-C_{20})-alkyl or cycloalkylalkyl,

R_4 is phenyl, (C_1-C_{20})-alkylphenyl or (C_1-C_{20})-alkyl which is optionally substituted with -OH, (C_1-C_{20})-alkyloxy or halogen,

R_{11} is (C_1-C_5)-alkyl, preferably methyl or ethyl, which is optionally substituted with

R_{12} and R_{13} are independently of each other either hydrogen or (C_1-C_5)-alkyl, preferably methyl or ethyl, optionally substituted.

6. The compound of claim 3, wherein

R_1 and R_2 are hydrogen, R_4 is 1,2-dihydroxypropyl and R_{11} is methyl or ethyl and R_{12} and R_{13} are independently of each other either hydrogen or methyl.

7. The compound of claim 5, wherein

R_1 is cycloalkylalkyl, optionally substituted with (C_1-C_5)-alkyl, or (C_1-C_5)-O-alkyl,

R_2 is hydrogen,

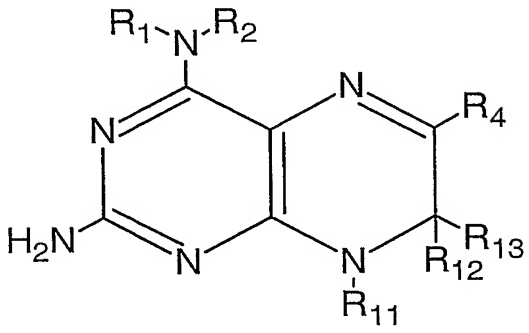
R_4 is 1,2-dihydroxypropyl and

R_{12} and R_{13} are independently of each other either hydrogen or methyl.

8. The compound of claim 7, wherein R_1 is cyclohexylmethyl or cyclohexylethyl.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of a compound according to any of claims 1-8, or a pharmaceutically acceptable acid addition salt thereof.

10. Use of a compound of formula I:



(I)

for treating a disorder associated with an increased NO level, wherein in formula (I)

R_1 is hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkenyl, (C_1-C_{20})alkynyl, preferably (C_1-C_{10})-alkyl, cycloalkyl, cycloalkenyl, preferably (C_3-C_8)-cycloalkyl, cycloalkylalkyl, aryl, alkylaryl, preferably (C_1-C_3)-alkylaryl or arylalkyl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6,

R_2 is, independently of R_1, hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkenyl, (C_1-C_{20})-alkynyl, preferably (C_1-C_{10})-alkyl, cycloalkyl, cycloalkenyl, preferably (C_3-C_8)-cycloalkyl, cycloalkylalkyl, aryl, alkylaryl, preferably (C_1-C_3)-alkylaryl, or arylalkyl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6,

R_1 and R_2 may, together with the nitrogen atom bearing them, form a 3-8-membered ring which may optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and which is optionally substituted by one or more radicals, preferably R_6 radicals,

R_4 is (C_1-C_{20})-alkyl, (C_1-C_{20})-alkenyl, (C_1-C_{20})-alkynyl, preferably (C_1-C_{10})-alkyl, cycloalkyl, cycloalkenyl, preferably (C_3-C_8)-cycloalkyl, cycloalkylalkyl, aryl or alkylaryl, preferably (C_1-C_3)-alkylaryl, arylalkyl, -CO-O-alkyl, preferably -CO-O-(C_1-C_5)-alkyl, -CO-O-aryl, -CO-alkyl, preferably -CO-(C_1-C_5)-alkyl or -

CO-aryl, where the organic radicals, preferably the alkyl and aryl radicals, may be substituted by one or more substituents, in particular by substituents R_7,

R_6 is -F, -Cl, -Br, -I, -OH, -O-(C_1-C_{10})-alkyl, -O-phenyl, -O-CO-(C_1-C_{10})-alkyl, -O-CO-aryl, -NR_8R_9, oxo, phenyl, -CO-(C_1-C_5)-alkyl, -CF_3, -CN, -$CONR_8R_9$, -COOH, -CO-O-(C_1-C_5)-alkyl, -CO-O-aryl, -$S(O)_n$-(C_1-C_5)-alkyl, -SO_2-NR_8R_9,

R_7 has, independently of R_6, one of the meanings of R_6,

R_8 is hydrogen or (C_1-C_{20})-alkyl, preferably (C_1-C_5)-alkyl,

R_9 is hydrogen, (C_1-C_{20})-alkyl, preferably (C_1-C_5)-alkyl or aryl, preferably phenyl,

R_{11} is hydrogen, (C_1-C_{20})-alkyl, (C_1-C_{20})-alkylaryl, preferably (C_1-C_5)-alkyl, aryl, arylalkyl, -CO-alkyl, -CO-aryl, where the organic radicals, preferably the alkyl and/or aryl radicals, may be substituted by one or more substituents, preferably by substituents R_6

R_{12} is hydrogen, (C_1-C_5)-alkyl, aryl, -O-(C_1-C_{10})-alkyl, -O-phenyl, -O-CO-(C_1-C_{10})-alkyl, -O-CO-aryl, -NR_8R_9, phenyl, -CO-(C_1-C_5)-alkyl, -CF_3, -CN, -$CONR_8R_9$, -COOH, -CO-O-(C_1-C_5)-alkyl, -CO-O-aryl, -F or –Cl

R_{13} has, independently of R_{12}, one of the meanings of R_{12}

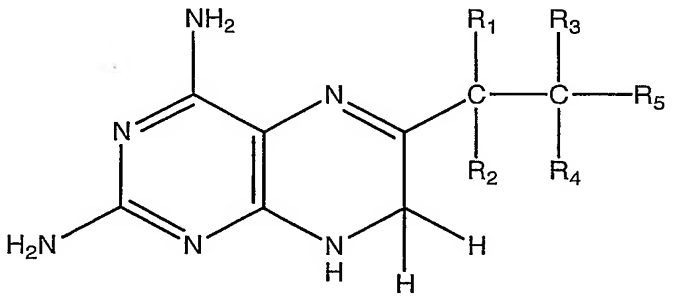
aryl is preferably phenyl, naphthyl or heteroaryl, each of which may be unsubstituted or substituted, for example may be substituted by one or more identical or different substituents from the series halogen, (C_1-C_{20})-alkyl, preferably (C_1-C_5)-alkyl or phenyl, -OH, -O-(C_1-C_{20})-alkyl, preferably -O-(C_1-C_5)-alkyl, (C_1-C_{20})-alkylenedioxy, preferably (C_1-C_2)-alkylenedioxy, -N_8R_9, -NO_2, -CO-(C_1-C_5)-alkyl, -CF_3, -CN, -$CONR_8R_9$, -COOH, -CO-O-(C_1-C_5)-alkyl, -$S(O)_n$-(C_1-C_5)-alkyl, -SO_2-NR_8R_9,

heteroaryl is a 5- to 7-membered unsaturated heterocycle which contains one or more heteroatoms from the series O, N, S,

n is 0, 1 or 2,

in all their stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and their physiologically tolerated salts, hydrates and esters

with the proviso that compounds of the formula (Ia)



(Ia) are excluded,

wherein in formula (Ia) R_1, R_2, R_3 and R_4 are independently from each other H or OH, R_5 is H, CH_3, CH_2OH, CHO or a lower (C_1-C_9) alkyl radical, which can be a straight or a branched chain, as well as $(CH(OH))_n$-Y or $(CH(OH))_n$-$(CH_2)_m$-W, wherein Y is hydrogen or a lower alkyl (C_1-C_9) radical, W is hydrogen or a hydroxyl group, an n and m are independently from each other 1-20.

11. The use of claim 10, wherein in the compound of formula (I)

R_1 is hydrogen,

R_2 is hydrogen, (C_1-C_{20})-alkyl or cycloalkylalkyl,

R_4 is phenyl, (C_1-C_{20})-alkylphenyl or (C_{12}-C_{20})-alkyl which is optionally substituted with -OH, alkyloxy or halogen, and wherein

R_{11}, R_{12} and R_{13} are independently of each other either hydrogen or methyl.

12. The use of claim 11, wherein in the compound of formula (I)

R_1 is cycloalkylalkyl, optionally substituted with (C_1-C_5)-alkyl, or (C_1-C_5)-O-alkyl,

R_2 is hydrogen,

R_4 is 1,2-dihydroxypropyl and

R_{11}, R_{12} and R_{13} are independently of each other either hydrogen or methyl.

13. The use of claim 12, wherein in the compound of formula (I) R_1 is cyclohexylmethyl or cyclohexylethyl.

14. The use of claim 10, wherein in the compound of formula (I)

R_1 is hydrogen,

R_2 is hydrogen, (C_1-C_{20})-alkyl or cycloalkylalkyl,

R_4 is phenyl , (C_1-C_{20})-alkylphenyl or (C_1-C_{20})-alkyl which is optionally substituted with -OH, (C_1-C_{20})-alkyloxy or halogen,

R_{11} is (C_1-C_5)-alkyl, preferably methyl or ethyl, which is optionally substituted with

R_{12} and R_{13} are independently of each other either hydrogen or (C_1-C_5)-alkyl, preferably methyl or ethyl, optionally substituted.

15. The use of claim 14, wherein in the compound of formula (I)

R_1 and R_2 are hydrogen, R_4 is 1,2-dihydroxypropyl and R_{11}, is methyl or ethyl and R_{12} and R_{13} are independently of each other either hydrogen or methyl.

16. The use of claim 15, wherein in the compound of formula (I)

R_1 is cycloalkylalkyl, optionally substituted with (C_1-C_5)-alkyl, or (C_1-C_5)-O-alkyl,

R_2 is hydrogen,

R_4 is 1,2-dihydroxypropyl and

R_{12} and R_{13} are independently of each other either hydrogen or methyl.

17. The use of claim 16, wherein in compound of formula (I) R_1 is cyclohexylmethyl or cyclohexylethyl.

18. The use of any of claims 10-17, wherein said disorder associated with an increased NO level is selected from the group consisting of:

(a) disorders characterized by pathological blood pressure decreases, such as occur in septic or hemorrhagic shock, in tumor or cancer therapy with cytokines or in cirrhosis of the liver;

(b) inflammatory disorders, such as rheumatoid arthritis and in particular ulcerative colitis;

(c) insulin-dependent diabetes mellitus;

(d) transplant rejection reactions;

(e) cardiovascular disorders, such as arteriosclerosis, post-ischemic tissue damage and infarct damage, reperfusion damage, myocarditis based on a Coxsackie virus infection and cardiomyopathy;

(f) disorders of the nervous system/central nervous system, such as stroke, multiple sclerosis, traumatic brain injury, migraine, neuritides of varying etiogeneses, encephalomyelitides, viral neurodegenerative disorders, Alzheimer's disease, hyperalgesia and epilepsy;

(g) disorders of the kidney, such as acute kidney failure and nephritides of varying etiogeneses, in particular glomerulonephritis.

19. The use of any of claims 10-18 for the treatment of a mammal, especially a human.

20. A method of treating a subject having a disorder associated with an increased NO level, comprising administering to the subject a therapeutically sufficient amount of the compound of any of claims 1-8.

21. The method of claim 20, wherein said disorder associated with an increased NO level is selected from the group consisting of:

(a) disorders characterized by pathological blood pressure decreases, such as occur in septic or hemorrhagic shock, in tumor or cancer therapy with cytokines or in cirrhosis of the liver;

(b) inflammatory disorders, such as rheumatoid arthritis and in particular ulcerative colitis;

(c) insulin-dependent diabetes mellitus;

(d) transplant rejection reactions;

(e) cardiovascular disorders, such as arteriosclerosis, post-ischemic tissue damage and infarct damage, reperfusion damage, myocarditis based on a Coxsackie virus infection and cardiomyopathy;

(f) disorders of the nervous system/central nervous system, such as stroke, multiple sclerosis, traumatic brain injury, migraine, neuritides of varying etiogeneses, encephalomyelitides, viral neurodegenerative disorders, Alzheimer's disease, hyperalgesia and epilepsy;

(g) disorders of the kidney, such as acute kidney failure and nephritides of varying etiogeneses, in particular glomerulonephritis.

22. The method of claim 20 or 21, wherein said subject is a mammal, especially a human.